UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,187	10/31/2005	Dharmaraj Ramachandra Rao	TPP 31767	2383

24257 7590 09/08/2006

STEVENS DAVIS MILLER & MOSHER, LLP
1615 L STREET, NW
SUITE 850
WASHINGTON, DC 20036

EXAMINER	
YOUNG, SHAWQUIA	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 09/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/535,187	RAO ET AL.	
	Examiner	Art Unit	
	Shawquia Young	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22,23,25 and 26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-6,8-10 and 12-15* is/are allowed.

6)☒ Claim(s) *16-20,22,23,25 and 26* is/are rejected.

7)☒ Claim(s) *7 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

FIRST ACTION ON THE MERITS

Claims 1-20, 22-23, and 25-26 are currently pending in the instant application. Claims 21 and 24 were cancelled by preliminary amendment.

I. *Priority*

The instant application is a 371 of PCT/GB03/04981, filed on November 18, 2003, which claims benefit of Foreign Application UNITED KINGDOM 0226885.2, filed on November 18, 2002.

II. Information Disclosure Statement

The information disclosure statements (IDS) submitted on March 16, 2006 and August 7, 2006 have been considered by the examiner. See Applicant's copies of the 1449.4

III. Rejection(s)

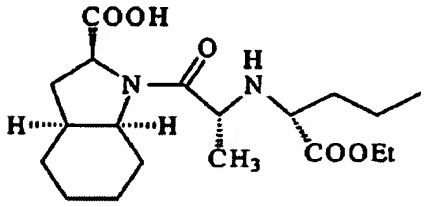
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

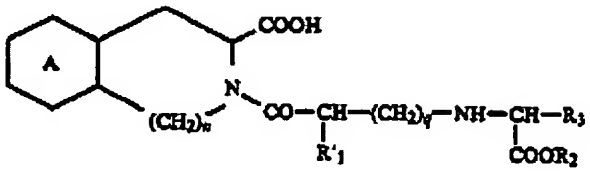
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(1) Claims 16 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by *Vincent, et al.*, US Pat. No. 4,508,729. Claim 16 is a product by process claim and the determination of patentability is based on the product itself and does not depend on its method of production. In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Also see M.P.E.P. 2113. The instant invention of claim 16 is a pharmaceutically acceptable salt of perindopril optionally in hydrated form with the structure



. The instant invention of claim 23 is a pharmaceutical composition comprising a pharmaceutically acceptable salt of perindopril according to claim 16, together with one or more pharmaceutically acceptable carriers, diluents or excipients thereof.

The *Vincent, et al.* reference teaches substituted azabicycloalkanedicarboxylic acids and the salts thereof with the genus structure



wherein R_1 is a lower alkyl group and can carry an amino group, R_2 is hydrogen or a lower alkyl group, R_3 is a straight or branched alkyl group, a mono- or di-cycloalkylalkyl or phenylalkyl group having no more than a total of 9 carbon atoms, or a substituted alkyl group, the ring A is saturated and n=0 or 1, the ring A is a benzene ring and n=1. One of the species taught by *Vincent, et al.* is the sodium salt of the above structure wherein A is saturated and n=0, R_1 is CH_3, R_2 is C_2H_5, q=0,and R_3 is n-C_3H_7 (See Table, column 13, compound 17). This species taught by the reference anticipates a pharmaceutically acceptable salt of perindopril optionally in hydrated form claimed in claim 16 of the instant invention. The reference also teaches a pharmaceutical composition containing at least one compound according to the above genus structure in conjuction with an inert, non-toxic pharmaceutically-acceptable carrier or excipient (See claim 4, column 18, line 10). The pharmaceutical composition comprising specifically compound 17 taught by *Vincent, et al.* anticipates the claimed pharmaceutical composition in claim 23 in the instant invention.

(2) Claims 25 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by *Straub, et al.*, U.S. Pat. No. 6,932,983. The instant invention of claims 25 and 26 are to a method of inhibiting ACE in a patient in need thereof comprising administering a pharmaceutically acceptable salt of perindopril and a method of manufacturing a

medicament for inhibiting ACE comprising a pharmaceutically acceptable salt of perindopril of claim 16.

The *Straub, et al.* reference teaches methods of manufacturing porous drug matrices and methods of delivering the drug to a patient in need thereof. One of the species of administered drugs taught by *Straub, et al.* is perindopril (See claim 17, column 24, line 8). This species taught by the primary reference anticipates a method of inhibiting ACE in a patient in need thereof comprising administering a pharmaceutically acceptable salt of perindopril and a method of manufacturing a medicament for inhibiting ACE comprising a pharmaceutically acceptable salt of perindopril in claims 25 and 26.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) that forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

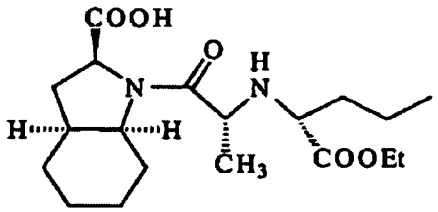
Graham v. John Deere Co. set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. §103(a). *See Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). Specifically, the analysis must employ the following factual inquiries:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 17-20 and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Vincent, et al.* (04/508729, 1985). It is well established that "something which is old does not become patentable upon the discovery of a new property". In re Grasselli, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983).

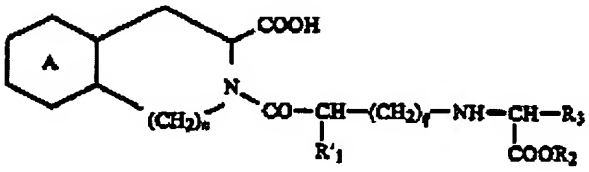
Applicants claim a pharmaceutically acceptable salt of hydrated perindopril with



the structure $\cdot nH_2O$ wherein n is an integer of 1 to 5, or a reciprocal of integers 2 to 5.

The Scope and Content of the Prior Art (MPEP §2141.01)

The *Vincent, et al.* reference teaches substituted azabicycloalkanedicarboxylic acids and the salts thereof with the genus structure



wherein R_1 is a lower alkyl group and can carry an amino group, R_2 is hydrogen or a lower alkyl group, R_3 is a straight or branched alkyl group, a mono- or di-cycloalkylalkyl or phenylalkyl group having no more than a total of 9 carbon atoms, or a substituted alkyl group, the ring A is saturated and n=0 or 1, the ring A is a benzene ring and n=1. One of the species taught by *Vincent, et al.* is

the sodium salt of the above structure wherein A is saturated and n=0, R_1 is CH_3, R_2 is C_2H_5, q=0,and R_3 is n-C_3H_7 (See Table, column 13, compound 17).

The Difference Between the Prior Art and the Claims (MPEP §2141.02)

The difference between the prior art of *Vincent, et al.* and the instant invention is that the applicants are claiming the hydrated form of a pharmaceutically acceptable salt of perindopril whereas the prior art teaches a pharmaceutically acceptable salt of perindopril.

Prima Facie Obviousness-The Rational and Motivation (MPEP §2142-2413)

In In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977), it was established that the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. Adding water to a product via hydration, which is inherently present does not result in a patentably distinct invention. The motivation to optimize the compounds and process of *Vincent, et al.* would be to prepare similar compounds that have similar pharmacological properties, i.e. ACE inhibitors useful in treating cognitive disorders. Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to isolate the hydrated form of a pharmaceutically acceptable salt of perindopril.

Claim Rejections - 35 USC § 112

(1) The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 25, and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case,

The nature of the invention

The nature of the invention of claims 23, 25 and 26 is a pharmaceutical composition comprising an effective ACE inhibitory amount, a method for inhibiting ACE in a patient in need, and a method of manufacturing a medicament for inhibiting ACE.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art

would recognize that in regards to therapeutic effects of cognitive disorders by inhibiting ACE would make a difference.

Applicants are claiming methods of inhibiting ACE in a patient in need. Further, applicants fail to identify diseases or disorders that can be treated by inhibiting ACE by using the claimed invention.

Applicants' claims are therefore drawn to a method of inhibiting ACE in a patient in need, a pharmaceutical composition comprising an effective ACE inhibitory amount of claimed products, and a method of manufacturing a medicament for inhibiting ACE. Various diseases and disorders (i.e. hypertension, cognitive disorders, cardiovascular disorders, etc.) can be treated by ACE inhibitors (See e.g. Das, 2005). Enablement for the scope of treating cognitive disorders and cardiovascular disorders by inhibiting ACE is not present in the specification. Cardiovascular disorders include hypertension, stroke, congestive heart failure, etc. Cognitive disorders include conditions such as delirium, Alzheimer's disease, Pick's disease, Parkinson's disease, Binswanger's disease, etc.

(URL:http://en.wikipedia.org/wiki/Category:Cognitive_disorders)

Furthermore, there is a vast range of causes for the problem and biochemical pathways that mediate cognitive disorders that affect the various nervous systems. There is no common mechanism by which all, or even most, cognitive disorders arise and one treatment cannot be used to treat all types of cognitive disorders.

Applicants' claims are therefore drawn to the treatment of Alzheimer's disease. It is the state of the art that there is no known cure or prevention for Alzheimer's disease

and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease. (URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html.)

In addition, Layzer, Cecil Textbook of Medicine (article enclosed), states that "some degenerative diseases are difficult to classify because they involve multiple anatomic locations" (see page 2050). Alzheimer's disease has traditionally been very difficult or impossible to prevent or even to treat effectively with chemotherapeutic agents (*See* e.g., the Cecil Textbood of Medicine, 20th edition (1996), Vol. 2, page 1994).

Applicants are also claiming a treatment of stroke. Stroke represents on of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics

and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Hence, in the absence of a showing of correlation between all the diseases encompassed by the claims as capable of treatment by inhibiting ACE one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability of the role of preventing neuronal death and, for example, since it is no known cure for Alzheimer's disease and treatment protocols for Alzheimer's disease depend on the stage of the disease.

The amount of direction present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the listing of several diseases applicant considers as treatable by the claimed invention found on pages 1 and 7. There are no working examples present for the treatment of any disease or disorder by inhibiting ACE.

Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The breadth of the claims

The breadth of the claims is drawn to pharmaceutical composition comprising an effective ACE inhibitory amount, a method for inhibiting ACE in a patient

in need including the treatment of cognitive disorders, and a method of manufacturing a medicament for inhibiting ACE.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all conditions such as cognitve disorders, hypertension, etc. would be benefited by the inhibition of ACE would furthermore then have to determine which of the claimed compounds in the instant invention would provide treatment of the diseases.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* or *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

The specification fails to provide sufficient support of the broad use of the claimed compounds of the invention in a method of inhibiting ACE. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the invention in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling

disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome, for example, by deleting the method claims.

(2) The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps need to show the method steps involved in the manufacturing of a medicament using a pharmaceutically acceptable salt of perindopril of claim 16 as shown in Example 7(b), page 12 of the specification.

IV. *Objections*

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because the abstract contains the term "said" which is legal phraseology. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 7 and 11 are objected to because of the following informalities: both claims 7 and 11 contain the misspelled term "chacoal". The correct spelling of the term should be "charcoal". Appropriate correction is required.

V. Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shawquia Young
Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600

Joseph McKane
Supervisory Patent Examiner
Art Unit 1626, Group 1620
Technology Center 1600